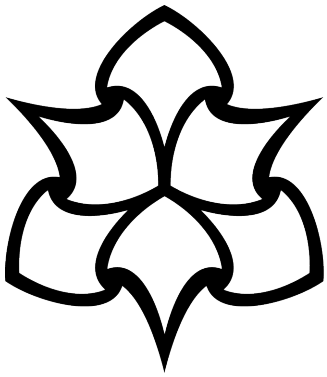

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Original Article

Associations between prenatal indicators of mechanical loading and proximal femur shape: findings from a population-based study in ALSPAC offspring

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Abstract

Objectives: Hip development is influenced by mechanical loading, but associations between prenatal loading and hip shape in later life remain unexplored. **Methods**: We examined associations between prenatal loading indicators (gestation length, oligohydramnios (OH) and breech) obtained from obstetric records and hip shape modes (HSMs) generated using dual-energy X-ray absorptiometry images taken at age 14- and 18-years in participants from the UK Avon Longitudinal Study of Parents and Children (ALSPAC). These associations were examined in 2453 (30 OH, 105 breech) and 2330 (27 OH, 95 breech) participants with complete data at age 14- and 18-years respectively using confounder-adjusted models. **Results**: At 14 years HSM2 was 0.59SD lower in OH males, and HSM5 (-0.31SD) and HSM9 (-0.32SD) were lower in OH in both sexes. At 18 years HSM1 (-0.44SD) and HSM2 (-0.71SD) were lower and HSM6 (0.61SD) and HSM8 (1.06SD) were higher in OH males, whilst HSM5 was lower in OH in both sexes. OH appeared to be associated with a wider femoral neck and head, and larger lesser/greater trochanters. Only weak associations were observed between gestation length/breech and HSMs. **Conclusions**: These results suggest that prenatal skeletal loading, in particular oligohydramnios, may influence adolescent joint shape with associations generally stronger in males.

Keywords: ALSPAC, Biomechanics, DXA, Growth, Pregnancy

Introduction

The prenatal period represents a period of dramatic change in the size and shape of the proximal femur. Following limb formation, from 12 weeks to 40 weeks of gestation femoral head diameter increases more than four-fold, whilst femoral torsion and inclination increase by around 40° and 7.5° respectively[1,2]. The relative magnitude of change in femoral head size over this prenatal period is similar to that experienced in the first two decades of postnatal life[3], after which little change is observed. Fetal changes in femoral neck-shaft angle[4,5] are also similar to those observed in the first decade of life, where childhood decreases in femoral torsion are only around 15° [6,7]. These features have clinical implications in later life as a larger femoral head[8], smaller neck-shaft angle[9] and greater femoral torsion[10] are associated with hip osteoarthritis, and large neck-shaft angles[11] are associated with increased hip fracture risk. Given the importance of the fetal period for femoral development and the clinical consequences of altered femoral shape, prenatal factors may influence risk of hip osteoarthritis and fracture in later life as a consequence of effects on fetal femoral development.

One factor thought to contribute substantially to prenatal joint development is mechanical loading caused by reaction and muscle forces during fetal movements

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such as kicking. Fetal kicking at around 30 weeks produces reaction forces on the uterine wall of 40-50N[12] which equates to 3-4 times fetal bodyweight. Because of the short lever arms muscles work with, muscle forces acting directly on the developing bones are several times greater than these external forces[13]. The importance of these movements for skeletal development can be seen in rare cases of neuromuscular conditions of fetal onset, which lead to slender, fracture-prone bones[14]. In addition, a number of less severe prenatal conditions have been identified which lead to restrictions in movement and result in lower stresses applied to bones. Breech (bottom-down) position of the fetus and oligohydramnios (low levels of amniotic fluid) occur in around 5% and 4-5% of pregnancies respectively, and result in fetal kick forces only 42% and 12% of that experienced by healthy fetuses of similar age[15]. Fetal loading and resultant stresses and strains during movement increase during gestation[12], such that pre-term birth would limit exposure to large kicking forces in utero.

Reduced mechanical loading in fetuses with the conditions described above, might be expected to alter hip shape and increase the risk of future hip pathology. Indeed, breech presentation is associated with 10° greater femoral anteversion[16] at birth, and smaller proximal femur area in early childhood[17]. Breech presentation is associated with greater risk of neonatal hip instability and developmental dysplasia of the hip (DDH)[18], as is longer gestational length, a further potential risk factor for reduced fetal mechanical loading. In addition, oligohydramnios is a key risk factor for DDH[19]. There is some evidence of associations between prenatal factors and clinical hip outcomes in adulthood, as preterm birth is associated with greater risk of hip shape abnormalities and hip osteoarthritis requiring total hip replacement in adulthood[20,21]. In addition, individuals born preterm with very low birthweight (<1500 g) have a greater neck-shaft angle than controls in young adulthood[22]. However, to our knowledge there are no prospective studies investigating whether, at a population level, prenatal factors are associated with clinically relevant features of hip shape in later childhood.

Statistical shape modelling (SSM) has been developed as a tool for describing variation in overall hip shape based on principal components analysis, having been found to predict both hip fracture[23] and hip osteoarthritis progression[24]. Though initially developed to analyse hip radiographs, we recently applied this method to analysing hip images obtained from DXA scans[25,26], including in adolescents[27]. In the present study we examined associations between factors associated with altered prenatal skeletal loading (oligohydramnios, gestation length and breech presentation), and hip shape in adolescence as assessed by SSM applied to DXA scan images obtained at ages 14 and 18. We hypothesised that these prenatal factors would be associated with differences in hip shape in adolescence.

Methods

Materials and methods

Study participants

Pregnant women resident in the former county of Avon (around the city of Bristol in the South West of England UK) with expected dates of delivery 1st April 1991 to 31st December 1992 were invited to take part in the study. The initial number of pregnancies enrolled was 14,541 and of these initial pregnancies, there was a total of 14,676 foetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age[28,29]. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/). The present study is prospective, relating fetal exposures to hip shape outcomes collected during research clinics at age 14 and 18 years. Of 11,351 individuals invited, 6,147 attended the clinic at age 14 years. Of 10,101 individuals invited, 5,217 attended the clinic at 18 years. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

Outcome, exposures and covariate data

Hip DXA scans, performed by GE Lunar Prodigy (Madison, WI, USA) at 14 year and 18 year clinics, were used to quantify the shape of the proximal femur (outcome variable in this study). Exposures considered in this study include gestation length (recorded in weeks), diagnosis of oligohydramnios recorded as a binary variable indicating whether or not this was noted in the clinical record at any time during pregnancy, and breech position recorded at onset of labour in obstetric notes. Participant age at attendance, in completed months, was calculated as the difference between the date of attendance and date of birth, for both 14 year and 18 year clinics. Data on sex were obtained from hospital birth records.

Statistical shape modelling

Statistical shape modelling was used to quantify the shape of the proximal femur from hip DXA scans. This method and data generation in ALSPAC have been described previously[30]. Briefly, using Shape software (University of Aberdeen) each image was marked with a set of landmark points, outlining the contour of proximal femur (including the acetabular eyebrow). Procrustes analysis was used to translate, rotate and scale the images to remove influences of size and orientation. Principal component analysis was then performed to generate independent orthogonal modes of variation (hip shape modes; HSMs). A pre-defined set of points, previously obtained from an adult reference population[31], was then applied to the adolescent data and HSMs were re-calculated.

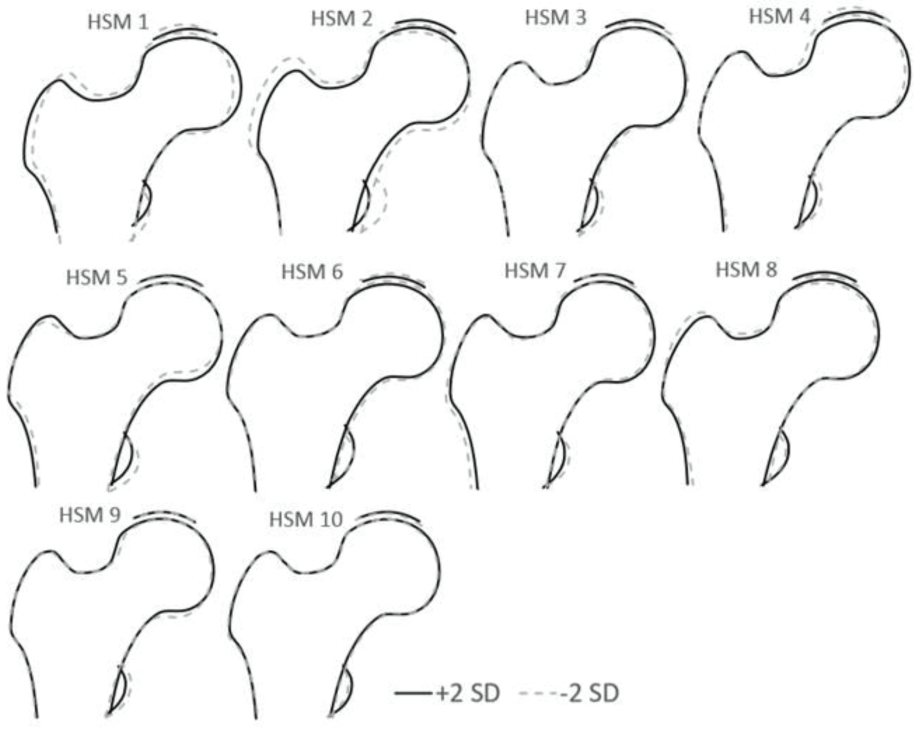

Figure 1. Variation in hip shape described by hip shape modes (HSMs) 1-10.

Each HSM describes in descending order percentage variation in the dataset. The first ten modes (HSM1-HSM10) collectively accounted for 85% of the total variance and were used as outcomes in the analysis (please refer to Figure 1 for graphical representation and our previous publication[30] for detailed description of the variation described by the top ten HSMs based on the adult reference SSM).

Statistical analysis

The normality of data was explored using descriptive statistics and histograms. Descriptive statistics are expressed as means with standard deviations (SD) for continuous variables and counts with percentages (%) for categorical variables. Multivariable linear regression was used to examine cross-sectional associations between prenatal exposures (gestation length as a continuous variable, and diagnosis of oligohydramnios and breech presentation as binary variables) and the top ten HSMs at age 14 and 18 years in a series of models. A priori, we considered gestation length (for oligohydramnios analysis), mother's age at delivery (gestation length analysis), and gestation length and parity (breech analysis) as potential confounders given plausible effects on the exposures and hip shape. We present unadjusted (model 1) and observed confounder adjusted models (model 2). We explored sex differences by comparing results (regression coefficients and their 95% confidence intervals) between males and females and by testing for evidence of a statistical interaction between sex and the exposures in relation to the associations with hip shape. As gestation length is a linear variable, we also included quadratic terms in models to test for deviation from linearity, but there was no evidence of non-linearity.

To illustrate the overall effect of each exposure on hip shape, coefficients from linear regression from all HSMs were simultaneously entered into Shape software, to produce composite hip shape figures representing changes associated with each exposure. Oligohydramnios and breech are binary variables, therefore results for these are differences in means comparing those with and without these outcomes; gestational age associations were per completed week older gestational age.

Results

Participant characteristics

Table 1 shows characteristics of participants at 14 and 18 year clinics. Of 6,147 children who attended the 14 year clinic, 2,453 (1,173 were male and 1,280 were female) had complete data on outcome and covariates (Figure 2). Their mean (SD) age was 13.8 (0.2) years. There were 30 oligohydramnios cases and 105 participants had a record of breech position at birth.

Of 5,217 individuals who attended the 18 year clinic, 2,330 (1,042 were male and 1,288 were female) had complete data on outcome and covariates. Mean (SD) age at clinic attendance was 17.8 (0.4) years, 27 participants had

Table 1. Descriptive statistics of ALSPAC study participants.

Variable		Age 14			Age 18		
		Combined (N=2,453)	Males (N=1,173)	Females (N=1,280)	Combined (N=2,330)	Males (N=1,042)	Females (N=1,288)
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age of participant (years)		13.8 (0.20)	13.8 (0.20)	13.8 (0.20)	17.8 (0.39)	17.8 (0.4)	17.8 (0.4)
BMI		20.4 (3.4)	20.0 (3.3)	20.7 (3.5)	22.9 (4.1)	22.8 (3.9)	22.9 (4.2)
Gestation length (weeks)		39.4 (2.0)	39.2 (2.1)	39.5 (1.8)	39.4 (1.9)	39.2 (2.0)	39.5 (1.8)
Maternal age (years)		29.3 (4.6)	29.4 (4.8)	29.2 (4.5)	29.3 (4.7)	29.6 (4.7)	29.1 (4.7)
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Oligohydramnios	Yes	30 (1.2)	17 (1.5)	13 (1.0)	27 (1.2)	12 (1.2)	15 (1.2)
	No	2423 (98.8)	1156 (98.6)	1267 (99.0)	2303 (98.8)	1030 (98.9)	1273 (98.8)
Breech at birth	Yes	105 (4.3)	42 (3.6)	63 (4.9)	95 (4.1)	39 (3.7)	56 (4.3)
	No	2348 (95.7)	1131 (96.4)	1217 (95.1)	2235 (95.9)	1003 (96.3)	1232 (95.7)
Parity	0	1303 (53.1)	632 (53.9)	671 (52.4)	1264 (54.3)	577 (55.4)	687 (53.3)
	1	785 (32.0)	362 (30.9)	423 (33.1)	724 (31.1)	308 (29.6)	416 (32.3)
	2	273 (11.1)	136 (11.6)	137 (10.7)	249 (10.7)	117 (11.2)	132 (10.3)
	3+	92 (3.8)	43 (3.7)	49 (3.8)	93 (4.0)	40 (3.8)	53 (4.1)
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Hip Shape Mode scores (HSMs)	HSM1	2.3 (0.4)	2.2 (0.4)	2.3 (0.4)	2.4 (0.4)	2.4 (0.4)	2.4 (0.4)
	HSM2	0.6 (0.7)	0.5 (0.8)	0.6 (0.7)	0.2 (0.9)	0.0 (0.8)	0.5 (0.8)
	HSM3	-0.2 (0.7)	-0.1 (0.7)	-0.3 (0.7)	0.1 (0.7)	0.0 (0.6)	0.2 (0.7)
	HSM4	0.9 (0.7)	0.7 (0.7)	1.0 (0.6)	0.4 (0.7)	0.3 (0.7)	0.4 (0.7)
	HSM5	-1.1 (0.8)	-1.1 (0.8)	-1.2 (0.8)	-1.5 (0.9)	-1.7 (0.8)	-1.3 (0.9)
	HSM6	0.3 (0.7)	0.4 (0.7)	0.2 (0.6)	0.3 (0.9)	0.6 (0.9)	0.0 (0.8)
	HSM7	-0.3 (0.6)	-0.4 (0.6)	-0.2 (0.6)	0.0 (0.7)	0.0 (0.6)	0.0 (0.7)
	HSM8	0.4 (1.0)	0.8 (0.9)	0.0 (0.9)	0.0 (0.9)	0.2 (0.9)	-0.1 (0.9)
	HSM9	0.2 (0.8)	0.2 (0.8)	0.3 (0.7)	-0.2 (0.9)	-0.5 (0.8)	0.0 (0.9)
	HSM10	-1.1 (0.6)	-1.1 (0.6)	-1.1 (0.6)	-1.0 (0.8)	-1.0 (0.8)	-1.1 (0.8)

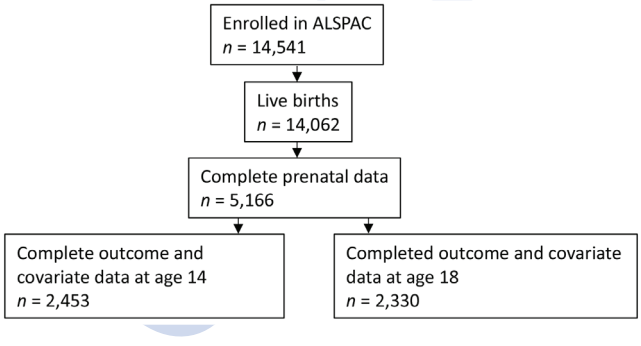

Figure 2. Flow diagram showing participant n at each stage of data preparation.

a diagnosis of oligohydramnios and 95 participants had a record of breech position at birth.

A total of 1,730 individuals (773 were male and 957 were female) attended both 14 year and 18 year clinics and had complete covariate and outcome data. Of those, 19 had a diagnosis of oligohydramnios and 78 participants had a record of breech position at birth.

Associations between prenatal factors and hip shape

Oligohydramnios

Age 14

In sex-combined unadjusted analysis, oligohydramnios was associated with HSM2, HSM5 and HSM9, with these associations essentially unchanged following adjustment for sex and gestation length (Table 2). There was some evidence of interaction by sex (in both models) for HSM2 ($p_{interaction}$=0.012), but no strong evidence for this with HSM5 and HSM9 ($p_{interaction}$=0.869 and 0.516, respectively).

In males, in both unadjusted and observed confounder adjusted analysis there was evidence for an association between oligohydramnios and HSM2 (Table 2). In females, there was some evidence to suggest an association with HSM9 (in both models (Table 2).

We modelled overall proximal femur shape in oligohydramnios cases vs. controls in males and females separately (Figure 3). In males exposed to oligohydramnios,

Table 2. Associations between oligohydramnios and the top ten HSMs in ALSPAC offspring in model 2 (adjusted for gestation length), presented as combined data and stratified by sex.

HSM	Age 14							Age 18						
	Combined (n = 2,453)		Males (n=1,173)		Females (n=1,280)		p_{int}			Males (n=1,042)		Females (n=1,288)		p_{int}
	RC	95% CI	RC	95% CI	RC	95% CI		RC	95% CI	RC	95% CI	RC	95% CI	
1	0.03	(-0.12, 0.18)	-0.06	(-0.27, 0.15)	0.17	(-0.05, 0.39)	0.097	-0.21	(-0.37, -0.04)	-0.44	(-0.69, -0.18)	-0.02	(-0.23, 0.19)	0.007
2	-0.27	(-0.55, -0.00)	-0.59	(-0.96, -0.21)	0.12	(-0.28, 0.52)	0.012	-0.26	(-0.57, 0.05)	-0.71	(-1.18, -0.24)	0.09	(-0.33, 0.51)	0.016
3	-0.1	(-0.35, 0.15)	-0.23	(-0.57, 0.11)	0.06	(-0.30, 0.42)	0.259	-0.07	(-0.32, 0.18)	-0.08	(-0.45, 0.29)	-0.05	(-0.38, 0.29)	0.733
4	-0.12	(-0.37, 0.12)	-0.21	(-0.55, 0.13)	-0.04	(-0.39, 0.32)	0.569	0.03	(-0.24, 0.31)	0.04	(-0.37, 0.45)	0.02	(-0.35, 0.39)	0.889
5	-0.31	(-0.60, -0.03)	-0.32	(-0.71, 0.07)	-0.29	(-0.71, 0.13)	0.869	-0.35	(-0.67, -0.03)	-0.24	(-0.69, 0.21)	-0.43	(-0.88, 0.03)	0.677
6	0.01	(-0.24, 0.26)	-0.02	(-0.38, 0.34)	0.05	(-0.30, 0.40)	0.75	0.07	(-0.24, 0.39)	0.51	(0.02, 1.01)	-0.26	(-0.66, 0.14)	0.019
7	-0.14	(-0.36, 0.09)	-0.16	(-0.46, 0.13)	-0.12	(-0.45, 0.22)	0.933	-0.14	(-0.40, 0.12)	-0.19	(-0.56, 0.18)	-0.11	(-0.48, 0.27)	0.815
8	-0.03	(-0.36, 0.30)	0.08	(-0.38, 0.54)	-0.11	(-0.58, 0.35)	0.736	0.55	(0.20, 0.91)	1.06	(0.51, 1.60)	0.19	(-0.27, 0.66)	0.036
9	-0.32	(-0.59, -0.05)	-0.3	(-0.67, 0.07)	-0.4	(-0.80, 0.00)	0.516	-0.21	(-0.55, 0.13)	-0.13	(-0.59, 0.33)	-0.29	(-0.77, 0.20)	0.526
10	-0.11	(-0.33, 0.11)	-0.08	(-0.38, 0.21)	-0.17	(-0.49, 0.16)	0.622	-0.01	(-0.31, 0.29)	0.09	(-0.36, 0.53)	-0.08	(-0.49, 0.32)	0.604

Abbreviations: HSM (hip shape mode), RC (regression coefficient), CI (confidence interval), pint (p-value for sex interaction). Table shows differences in mean HSM scores between oligohydramnios cases and controls, 95% CIs and p value. Positive and negative beta coefficients indicate higher and lower mean HSM scores, respectively in individuals with oligohydramnios, compared with those without.

Table 3. Associations between gestation length and the top ten HSMs in ALSPAC offspring in model 2 (adjusted for mother's age at delivery), presented as combined data and stratified by sex.

HSM	Age 14							Age 18						
	Combined (n = 2,453)		Males (n=1,173)		Females (n=1,280)		p_{int}	Combined (n = 2,330)		Males (n=1,042)		Females (n=1,288)		p_{int}
	SRC	95% CI	SRC	95% CI	SRC	95% CI		SRC	95% CI	SRC	95% CI	SRC	95% CI	
1	0.02	(0.00, 0.04)	0.03	(0.01, 0.05)	0	(-0.02, 0.03)	0.088	0.02	(-0.00, 0.03)	0.03	(0.00, 0.05)	0	(-0.02, 0.03)	0.14
2	0.02	(-0.01, 0.05)	0.02	(-0.02, 0.06)	0.02	(-0.02, 0.06)	0.922	0.02	(-0.02, 0.05)	0.01	(-0.03, 0.06)	0.02	(-0.03, 0.07)	0.82
3	0.02	(-0.01, 0.04)	0.02	(-0.02, 0.05)	0.02	(-0.02, 0.05)	0.991	0.01	(-0.02, 0.03)	0.03	(-0.01, 0.06)	-0.01	(-0.05, 0.02)	0.14
4	0.03	(0.00, 0.05)	0.02	(-0.02, 0.05)	0.04	(0.00, 0.08)	0.337	0.03	(-0.00, 0.06)	0.02	(-0.02, 0.06)	0.04	(-0.01, 0.08)	0.56
5	0.03	(-0.00, 0.06)	0.04	(-0.00, 0.08)	0.02	(-0.03, 0.06)	0.466	0.06	(0.03, 0.10)	0.08	(0.04, 0.13)	0.05	(-0.01, 0.10)	0.28
6	0.01	(-0.02, 0.03)	0.01	(-0.03, 0.05)	0	(-0.04, 0.04)	0.703	0.01	(-0.03, 0.04)	0.01	(-0.04, 0.06)	0	(-0.04, 0.05)	0.75
7	-0.02	(-0.04, 0.01)	-0.03	(-0.06, 0.01)	0	(-0.04, 0.03)	0.37	-0.01	(-0.04, 0.02)	-0.02	(-0.05, 0.02)	0	(-0.05, 0.04)	0.58
8	0.04	(0.00, 0.07)	0.07	(0.02, 0.12)	0	(-0.05, 0.05)	0.053	0.04	(-0.00, 0.07)	0.07	(0.01, 0.12)	0.01	(-0.05, 0.06)	0.11
9	-0.01	(-0.04, 0.02)	-0.04	(-0.08, 0.00)	0.03	(-0.01, 0.07)	0.026	0.02	(-0.01, 0.06)	0	(-0.04, 0.05)	0.05	(-0.01, 0.10)	0.21
10	-0.01	(-0.04, 0.01)	-0.02	(-0.06, 0.01)	0	(-0.04, 0.03)	0.343	0.02	(-0.01, 0.05)	0.02	(-0.02, 0.06)	0.02	(-0.03, 0.06)	0.95

Abbreviations: HSM (hip shape mode), SRC (standardised regression coefficient), CI (confidence interval), pint (p-value for sex interaction). Table shows results of linear regression analysis between standardized values of gestation length and the top ten HSMs. Standardised regression coefficients represent SD change in HSM per SD increase in gestation length, 95% CIs and p value.

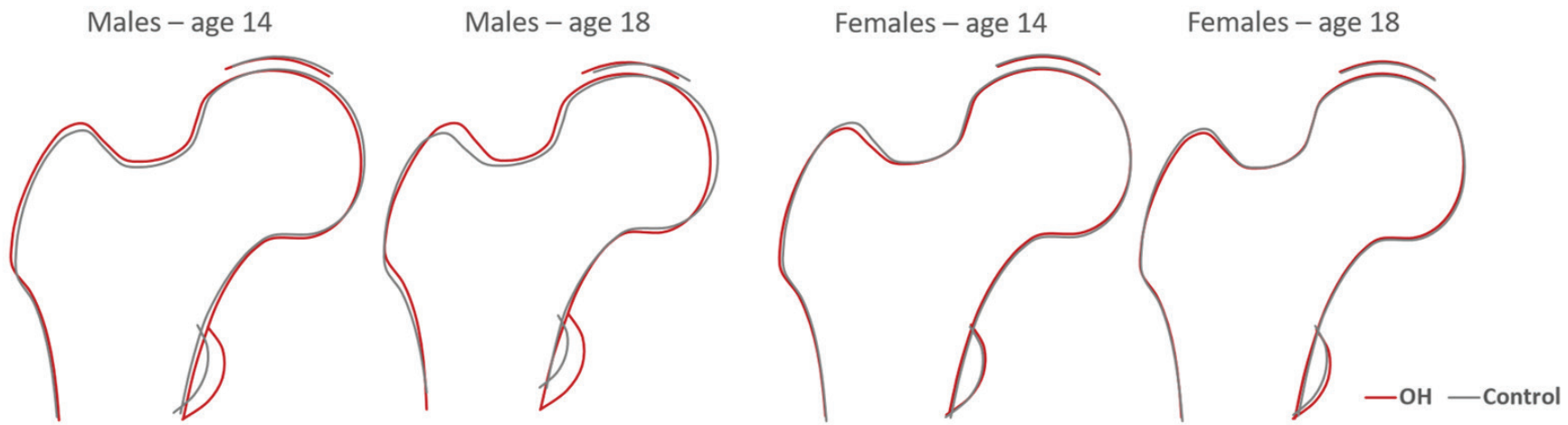

Figure 3. Composite hip shape figures representing differences in proximal femur shape at age 14 and 18 between individuals with and without oligohydramnios (OH), stratified by sex. Linear regression coefficients from all HSMs were simultaneously entered into Shape software, to model overall differences in hip shape.

Table 4. Associations between breech presentation and the top ten HSMs in ALSPAC offspring in model 2 (adjusted for gestation length and parity), presented as combined data and stratified by sex.

HSM	Age 14							Age 18						
	Combined (n = 2,453)		Males (n=1,173)		Females (n=1,280)		p_{int}	Combined (n = 2,330)		Males (n=1,042)		Females (n=1,288)		p_{int}
	RC	95% CI	RC	95% CI	RC	95% CI		RC	95% CI	RC	95% CI	RC	95% CI	
1	-0.01	(-0.10, 0.07)	-0.05	(-0.18, 0.09)	0	(-0.10, 0.11)	0.39	-0.08	(-0.17, 0.01)	-0.04	(-0.18, 0.10)	-0.11	(-0.23, -0.00)	0.585
2	-0.12	(-0.27, 0.02)	-0.19	(-0.43, 0.05)	-0.08	(-0.27, 0.10)	0.454	-0.06	(-0.23, 0.11)	-0.17	(-0.43, 0.09)	0.02	(-0.21, 0.24)	0.306
3	-0.03	(-0.17, 0.10)	-0.04	(-0.26, 0.18)	-0.03	(-0.20, 0.14)	0.866	-0.03	(-0.17, 0.10)	-0.07	(-0.27, 0.13)	-0.02	(-0.20, 0.16)	0.496
4	-0.11	(-0.24, 0.03)	-0.1	(-0.32, 0.11)	-0.11	(-0.27, 0.06)	0.889	-0.04	(-0.19, 0.10)	0	(-0.23, 0.23)	-0.07	(-0.27, 0.13)	0.616
5	-0.1	(-0.25, 0.06)	-0.3	(-0.55, -0.06)	0.04	(-0.16, 0.24)	0.025	0.03	(-0.15, 0.20)	0.02	(-0.23, 0.27)	0.02	(-0.22, 0.26)	0.88
6	0.04	(-0.10, 0.18)	0.12	(-0.11, 0.35)	-0.02	(-0.18, 0.15)	0.349	0.16	(-0.01, 0.32)	0.28	(0.00, 0.55)	0.07	(-0.14, 0.28)	0.249
7	-0.13	(-0.26, -0.01)	-0.17	(-0.36, 0.02)	-0.11	(-0.26, 0.05)	0.725	-0.03	(-0.18, 0.11)	-0.16	(-0.36, 0.05)	0.06	(-0.14, 0.26)	0.166
8	-0.01	(-0.19, 0.17)	-0.06	(-0.35, 0.24)	0.01	(-0.21, 0.23)	0.488	0.05	(-0.15, 0.24)	-0.03	(-0.34, 0.27)	0.09	(-0.16, 0.34)	0.397
9	-0.04	(-0.19, 0.11)	-0.09	(-0.33, 0.14)	0.01	(-0.18, 0.20)	0.718	0.04	(-0.14, 0.22)	-0.04	(-0.29, 0.22)	0.11	(-0.15, 0.37)	0.573
10	-0.08	(-0.19, 0.04)	-0.13	(-0.32, 0.06)	-0.04	(-0.19, 0.12)	0.569	0.02	(-0.14, 0.18)	-0.08	(-0.32, 0.17)	0.09	(-0.12, 0.31)	0.305

Abbreviations: HSM (hip shape mode), RC (regression coefficient), CI (confidence interval),pint (p-value for sex interaction). Table shows differences in mean HSM scores between oligohydramnios cases and controls, 95% CIs and p value. Positive and negative beta coefficients indicate higher and lower mean HSM scores, respectively in individuals with breech presentation, compared with those without.

the femoral neck appeared wider, lesser and greater trochanters were larger and femoral head extended in superolateral and inferomedial aspects. Whilst in females, the greater trochanter appeared smaller.

Age 18

In sex-combined unadjusted analysis, oligohydramnios was associated with HSM1, HSM5 and HSM8 and following adjustment for sex and gestation length associations were essentially unchanged, except HSM5 estimate which attenuated slightly (Table 3). There was some evidence of interaction by sex (in both models) for HSM1, HSM2, HSM6 and HSM8 (all $p_{interaction}<0.05$).

In males, there was evidence of consistent associations with HSM1 and HSM2 in both unadjusted and adjusted analyses, whereas association with HSM8 was strengthened following adjustment. In females, there was no evidence of an association between oligohydramnios and proximal femur shape (Table 3).

Compared with age 14, when modelling overall proximal femur shape at age 18 according to oligohydramnios diagnosis, in males the differences between cases and controls appeared more pronounced whereas in females the greater trochanter appeared smaller and lesser trochanter was larger (Figure 3).

Gestation length

Age 14

In sex-combined analysis, there were consistent associations (in terms of magnitude of effect) between gestation length and HSM1 and HSM4 (unadjusted and adjusted). There was no evidence for an unadjusted association with HSM8, but following adjustment an association emerged (Table 4). There was some evidence for sex interaction for HSM8 (unadjusted $p_{interaction}=0.053$) and HSM9 (unadjusted and adjusted $p_{interaction}<0.05$) and while there was no evidence to suggest interaction by sex with the remaining modes tested (all $p_{interaction}>0.3$), some differences in the effect estimates were observed in sex-stratified analysis. In males, gestation length was associated with HSM1 and HSM8, whereas in females it was associated with HSM4 (unadjusted and adjusted) (Table 4).

We modelled overall proximal femur shape in individuals born preterm (before 37 weeks gestation) vs. full-term, in males and females separately (Supplementary Figure 1). In males, no differences in hip shape were discernible, whereas in females the lesser trochanter appeared larger in those born preterm compared with full-term females.

Age 18

In sex-combined unadjusted analysis, gestation length was associated with HSM2, HSM4, HSM5 and HSM9 (model 1). Following adjustment these associations attenuated towards the null, except association with HSM5 which remained (Supplementary Table 2). In sex-stratified unadjusted and adjusted analysis, there was no strong evidence of sex interactions ($p_{interaction}=0.1$ in all cases). However, gestation length was associated with HSM1, HSM5 and HSM8 in males whereas no evidence of an association with any HSM was found in females (Table 5). When modelling the effect of preterm birth vs. full-term on hip shape at age 18, there was no discernible difference in females, whereas in males the lesser trochanter appeared slightly larger in those born preterm (Supplementary Figure 1).

Breech presentation

Age 14

In sex-combined analysis there was no strong statistical evidence to suggest an association between breech and hip shape and some evidence of sex interaction with HSM5 ($p_{interaction}=0.025$; Table 4) driven by the association between breech and HSM5 in males, with little evidence for association in females (unadjusted and adjusted analyses) (Table 4).

On modelling overall proximal femur shape in breech cases vs. controls, in males, the lesser trochanter appeared larger whereas there were no discernible differences in females (Supplementary Figure 2).

Age 18

In sex-combined unadjusted analysis there was weak evidence of an association between breech and HSM1, this association attenuated towards the null following adjustment (Table 4). In sex-stratified unadjusted analyses, there was no strong evidence for sex interaction (all $p_{interaction}>0.1$).

Similarly to age 14 results, when modelling overall proximal femur shape at age 18, the lesser trochanter appeared larger in males born with breech presentation, whereas there was no discernible difference in females (Supplementary Figure 2).

Discussion

The aim of this study was to examine whether prenatal factors potentially affecting mechanical loading in utero are associated with adolescent hip shape as assessed by SSM. Oligohydramnios and gestation length were associated with differences in hip shape at both 14 and 18 years of age. More pronounced associations were evident with oligohydramnios at the later timepoint, whilst associations with gestation length were consistent across both timepoints. Whilst some associations were evident across sexes, in a number of cases sex interactions indicated associations in males only. The differences in hip shape were notable in the case of boys born to mothers with oligohydramnios, in whom >0.5 SD differences were observed in HSM2 across both timepoints, and >1 SD difference in HSM8 was observed at 18 years.

To the best of our knowledge, this is the first prospective study to examine associations between prenatal factors related to skeletal loading in utero (oligohydramnios, breech presentation and gestational length) and hip shape in adolescence. Whereas oligohydramnios is known to be a

risk factor for DDH[19], the latter generally reflects femoral head and/or acetabular changes, whereas we observed an association with overall width relative to height of the upper femur, and size of the lesser trochanter. Conceivably, these shape differences could be associated with altered biomechanics, with implications for future risk of hip fracture and/or osteoarthritis. On the other hand, we recently found that greater size of the lesser trochanter, which may be a marker of incomplete internal rotation, and which was also associated with oligohydramnios and to a lesser extent with shorter gestation length, is associated with an increased risk of hip osteoarthritis in older men (B Faber et al, manuscript under review).

Gestation length was previously reported to be associated with femoral head size in fetuses at late gestational age[1], and given the similar associations observed in the present study, taken together, these findings suggest that this relationship persists into later life. Preterm birth has also been identified as a risk factor for hip joint replacement, with a hazard ratio of 2.0[21], which could conceivably be mediated by altered hip shape as identified in the current study. In addition, a previous study of young adults born preterm with very low birthweight found a greater neck-shaft angle in these individuals[22], but there was little evidence of similar associations in the current study. There was little evidence of associations between breech presentation and hip shape in adolescents of either sex.

Associations observed in this study may be attributable to altered mechanical loading of the developing skeleton during pregnancy. Stresses on the lower limbs caused by fetal movements increase throughout pregnancy[12], such that children with a shorter gestation length are not exposed to the largest loads evident in late pregnancy. Musculoskeletal modelling of the fetal environment suggests that oligohydramnios is associated with substantially reduced lower limb strains[15]. The consistent associations between gestation length and hip shape modes between early and late adolescence are supportive of a persisting shape difference evident through childhood. In contrast, associations between oligohydramnios and hip shape modes appeared stronger in late compared to early adolescence. This may support indirect effects of this exposure on biomechanics and later development, although the small number of participants with this exposure limits our confidence in this interpretation. Less marked differences in loading and consequently neonatal hip shape[16] were evident in breech compared to cephalic presentation. That no associations between breech presentation and hip shape were observed in the current study may suggest that only marked differences in prenatal mechanical loading (as evident in oligohydramnios) result in long-term differences in hip shape. This lack of association may also reflect the fact that breech was only examined at onset of labour, whereas up to 45% of children will have some exposure to breech position from second trimester onwards[32].

The majority of associations between prenatal factors and hip shape which we observed were stronger in males. Particularly in the case of associations between oligohydramnios and hip shape modes, findings were supported by strong statistical evidence for a sex interaction. Although the explanation for this apparent sex difference is unclear, it's conceivable that any tendency for narrower hips in girls born to mothers with oligohydramnios is reversed in later childhood, as part of pelvic widening following puberty in girls, which likely contributes to observed sex differences in hip shape present at age 18 years (M Frysz et al, manuscript under review). Examination of similar associations in prepubertal cohorts could explore this possibility. In addition, these findings are consistent with the sex-specific associations between early post-natal loading i.e. infant motor development and both bone[33,34] and joint shape[35] development we have observed previously where associations were more marked in males.

Strengths and weaknesses

This study examined a large cohort, in which information on a number of exposures and potential confounders had been obtained prospectively. Whilst large differences were noted between males with and without oligohydramnios, this was based on a small number of individuals exposed to oligohydramnios and this study requires replication in a larger cohort. Complete data were not available for all participants, therefore there may be a selection bias in those individuals included in the study. In addition, as the ALSPAC cohort are mostly white European and from more affluent families than the UK as a whole, results may not generalise to other ethnic groups and less affluent populations. We had no information on duration or severity of oligohydramnios, as only diagnosis at any time during pregnancy was recorded. Similarly, the duration of exposure to breech position during pregnancy was not recorded as this was only noted at the time of delivery. Given that up to 45% of children born cephalic occupy a breech position at some point in mid-late pregnancy[32] we may have underestimated the effects of prolonged breech position on hip shape. There is some suggestion that the type of breech position i.e. whether knees and hips are flexed or extended has effects on skeletal outcomes[36], but breech position type was not recorded. Therefore, future studies assessing whether duration and severity of breech and oligohydramnios influence associations with skeletal health are warranted. Importantly, given this is a single study with relatively small numbers (e.g. the association of oligohydramnios with hip shape in boys is based on 1,173 boys at 14 years and 1,042 boys at 18 years in whom 17 and 12 were exposed to oligohydramnios, respectively) all of the results presented here require replication in large independent studies. We did not take account of multiple testing (i.e. 10 associations were examined for each exposure and timepoint (i.e. 60 unadjusted and 60 observed confounder adjusted associations). Whilst these associations are not all independent of each other this does highlight further that our findings need to be treated with caution until replicated in a large study.

Conclusions

In adolescents, prenatal factors associated with altered fetal skeletal loading (namely gestation length and oligohydramnios) were associated with differences in hip shape and these associations were robust to adjustment for observed confounders. Associations between these exposures and hip shape were generally greater in males, particularly in individuals exposed to oligohydramnios. In contrast, there was little statistical support for associations between breech presentation and hip shape in either sex. These results suggest that prenatal skeletal loading may influence adolescent hip joint shape particularly in males, which could conceivably have long-term consequences for risk of hip fracture or osteoarthritis. Further studies are needed to replicate these findings, and to examine whether hip shape changes associated with these prenatal exposures are related to future risk of hip osteoarthritis and/or fracture.

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Supplementary Table 1. Associations between oligohydramnios and the top ten HSMs in ALSPAC offspring in model 1 (unadjusted), presented as combined data and stratified by sex.

HSM	Age 14							Age 18						
	Combined (n = 2,453)		Males (n=1,173)		Females (n=1,280)		p_{int}	Combined (n = 2,330)		Males (n=1,042)		Females (n=1,288)		p_{int}
	RC	95% CI	RC	95% CI	RC	95% CI		RC	95% CI	RC	95% CI	RC	95% CI	
1	0	(-0.16, 0.15)	-0.11	(-0.32, 0.09)	0.17	(-0.05, 0.39)	0.07	-0.22	(-0.38, -0.06)	-0.48	(-0.72, -0.23)	-0.02	(-0.23, 0.19)	0.005
2	-0.3	(-0.57, -0.03)	-0.6	(-0.97, -0.24)	0.11	(-0.29, 0.51)	0.01	-0.27	(-0.60, 0.05)	-0.71	(-1.17, -0.25)	0.07	(-0.35, 0.49)	0.014
3	-0.1	(-0.35, 0.15)	-0.25	(-0.59, 0.08)	0.05	(-0.31, 0.41)	0.23	-0.08	(-0.32, 0.17)	-0.13	(-0.49, 0.23)	-0.04	(-0.37, 0.30)	0.716
4	-0.17	(-0.42, 0.07)	-0.23	(-0.56, 0.10)	-0.06	(-0.41, 0.30)	0.484	0	(-0.28, 0.27)	0	(-0.40, 0.40)	0	(-0.37, 0.37)	0.991
5	-0.33	(-0.61, -0.05)	-0.38	(-0.76, 0.00)	-0.3	(-0.72, 0.12)	0.781	-0.43	(-0.75, -0.10)	-0.4	(-0.84, 0.05)	-0.45	(-0.91, -0.00)	0.861
6	0.02	(-0.23, 0.27)	-0.04	(-0.39, 0.32)	0.05	(-0.30, 0.40)	0.726	0.06	(-0.27, 0.39)	0.47	(-0.02, 0.95)	-0.26	(-0.66, 0.14)	0.021
7	-0.13	(-0.35, 0.09)	-0.11	(-0.40, 0.18)	-0.12	(-0.45, 0.22)	0.986	-0.12	(-0.38, 0.14)	-0.15	(-0.51, 0.21)	-0.1	(-0.48, 0.27)	0.869
8	-0.01	(-0.36, 0.34)	-0.05	(-0.50, 0.41)	-0.11	(-0.58, 0.35)	0.847	0.5	(0.14, 0.85)	0.88	(0.35, 1.42)	0.19	(-0.28, 0.65)	0.054
9	-0.32	(-0.59, -0.05)	-0.22	(-0.58, 0.14)	-0.41	(-0.82, -0.01)	0.482	-0.23	(-0.58, 0.12)	-0.13	(-0.58, 0.32)	-0.32	(-0.80, 0.17)	0.577
10	-0.09	(-0.31, 0.12)	-0.04	(-0.33, 0.26)	-0.17	(-0.49, 0.16)	0.56	-0.03	(-0.33, 0.26)	0.04	(-0.39, 0.48)	-0.09	(-0.49, 0.31)	0.656

Abbreviations: HSM (hip shape mode), RC (regression coefficient), CI (confidence interval). Table shows mean differences in HSM scores between oligohydramnios cases and controls, 95% CIs and p value. Positive and negative coefficients indicate higher and lower mean HSM scores, respectively in individuals with oligohydramnios, compared with those without.

Supplementary Table 2. Associations between gestation length and the top ten HSMs in ALSPAC offspring in model 1 (unadjusted), presented as combined data and stratified by sex.

HSM	Age 14							Age 18						
	Combined (n = 2,453)		Males (n=1,173)		Females (n=1,280)		p_{int}	Combined (n = 2,330)		Males (n=1,042)		Females (n=1,288)		p_{int}
	SRC	95% CI	SRC	95% CI	SRC	95% CI		SRC	95% CI	SRC	95% CI	SRC	95% CI	
1	0.02	(0.01, 0.04)	0.03	(0.01, 0.05)	0	(-0.02, 0.03)	0.087	0.02	(-0.00, 0.03)	0.03	(0.00, 0.05)	0	(-0.02, 0.03)	0.14
2	0.02	(-0.01, 0.05)	0.02	(-0.02, 0.06)	0.02	(-0.03, 0.06)	0.841	0.03	(0.00, 0.07)	0.01	(-0.03, 0.06)	0.02	(-0.03, 0.07)	0.84
3	0.01	(-0.02, 0.04)	0.02	(-0.02, 0.06)	0.01	(-0.03, 0.05)	0.89	0.01	(-0.02, 0.04)	0.03	(-0.01, 0.06)	-0.02	(-0.05, 0.02)	0.12
4	0.03	(0.01, 0.06)	0.02	(-0.02, 0.05)	0.04	(0.00, 0.08)	0.371	0.03	(0.00, 0.06)	0.02	(-0.02, 0.06)	0.04	(-0.01, 0.08)	0.56
5	0.02	(-0.01, 0.06)	0.04	(-0.00, 0.08)	0.02	(-0.03, 0.06)	0.448	0.08	(0.04, 0.11)	0.08	(0.04, 0.13)	0.05	(-0.01, 0.10)	0.29
6	0	(-0.03, 0.03)	0.01	(-0.03, 0.05)	0	(-0.04, 0.04)	0.71	-0.02	(-0.05, 0.02)	0.01	(-0.04, 0.06)	0	(-0.04, 0.05)	0.89
7	-0.01	(-0.04, 0.01)	-0.03	(-0.06, 0.01)	0	(-0.04, 0.03)	0.372	-0.01	(-0.04, 0.02)	-0.02	(-0.05, 0.02)	0	(-0.05, 0.04)	0.62
8	0.01	(-0.02, 0.05)	0.07	(0.02, 0.12)	0	(-0.05, 0.05)	0.047	0.03	(-0.01, 0.06)	0.07	(0.01, 0.12)	0	(-0.05, 0.06)	0.11
9	0	(-0.03, 0.03)	-0.04	(-0.08, 0.00)	0.03	(-0.01, 0.07)	0.028	0.04	(0.00, 0.08)	0	(-0.04, 0.04)	0.05	(-0.01, 0.10)	0.21
10	-0.01	(-0.04, 0.01)	-0.02	(-0.06, 0.01)	0	(-0.04, 0.03)	0.359	0.01	(-0.02, 0.05)	0.02	(-0.02, 0.06)	0.01	(-0.03, 0.06)	0.88

Abbreviations: HSM (hip shape mode), SRC (standardised regression coefficients), CI (confidence interval). Table shows results of linear regression analysis between standardized values of gestation length and the top ten HSMs in male and female adolescents. Standardised regression coefficients represent SD change in HSM per SD increase in gestation length, 95% CIs and p value.

Supplementary Table 3. Associations between breech presentation at birth and the top ten HSMs in ALSPAC offspring in model 1 (unadjusted), presented as combined data and stratified by sex.

HSM	Age 14							Age 18						
	Combined (n = 2,453)		Males (n=1,173)		Females (n=1,280)		p_{int}	Combined (n = 2,330)		Males (n=1,042)		Females (n=1,288)		p_{int}
	RC	95% CI	RC	95% CI	RC	95% CI		RC	95% CI	RC	95% CI	RC	95% CI	
1	-0.02	(-0.10, 0.06)	-0.07	(-0.21, 0.06)	0	(-0.10, 0.10)	0.386	-0.09	(-0.18, -0.01)	-0.06	(-0.20, 0.08)	-0.11	(-0.22, -0.00)	0.58
2	-0.13	(-0.28, 0.01)	-0.2	(-0.44, 0.03)	-0.09	(-0.27, 0.10)	0.449	-0.05	(-0.23, 0.12)	-0.18	(-0.43, 0.08)	0	(-0.22, 0.22)	0.314
3	-0.06	(-0.20, 0.07)	-0.06	(-0.28, 0.16)	-0.04	(-0.20, 0.13)	0.862	-0.03	(-0.17, 0.10)	-0.1	(-0.30, 0.11)	0	(-0.18, 0.17)	0.495
4	-0.11	(-0.24, 0.02)	-0.12	(-0.33, 0.09)	-0.14	(-0.30, 0.03)	0.89	-0.06	(-0.21, 0.09)	-0.02	(-0.24, 0.21)	-0.1	(-0.29, 0.10)	0.597
5	-0.13	(-0.29, 0.02)	-0.33	(-0.58, -0.09)	0.02	(-0.17, 0.22)	0.024	0	(-0.18, 0.17)	-0.03	(-0.28, 0.22)	-0.01	(-0.25, 0.22)	0.942
6	0.02	(-0.12, 0.15)	0.11	(-0.12, 0.34)	-0.02	(-0.18, 0.14)	0.351	0.12	(-0.05, 0.30)	0.27	(-0.00, 0.54)	0.07	(-0.14, 0.27)	0.241
7	-0.11	(-0.23, 0.01)	-0.14	(-0.33, 0.04)	-0.1	(-0.26, 0.05)	0.732	-0.02	(-0.17, 0.12)	-0.15	(-0.35, 0.06)	0.06	(-0.14, 0.26)	0.159
8	-0.11	(-0.30, 0.08)	-0.12	(-0.41, 0.17)	0	(-0.21, 0.22)	0.49	0.01	(-0.19, 0.20)	-0.08	(-0.38, 0.23)	0.08	(-0.16, 0.33)	0.418
9	-0.02	(-0.17, 0.13)	-0.06	(-0.30, 0.17)	-0.01	(-0.19, 0.18)	0.72	0.05	(-0.14, 0.24)	-0.03	(-0.28, 0.23)	0.07	(-0.18, 0.32)	0.6
10	-0.06	(-0.18, 0.06)	-0.1	(-0.29, 0.08)	-0.03	(-0.18, 0.12)	0.575	0	(-0.16, 0.16)	-0.1	(-0.34, 0.15)	0.07	(-0.14, 0.28)	0.305

Abbreviations: HSM (hip shape mode), RC (regression coefficients), CI (confidence interval). Table shows results of linear regression analysis between breech presentation at birth and the top ten HSMs. Positive and negative coefficients indicate higher and lower mean HSM scores, respectively in individuals in breech presentation at birth, compared with those without breech presentation. Model 1: unadjusted, model 2: adjusted for sex, gestation length and parity.

Supplementary Figure 1. Composite hip shape figures representing differences in proximal femur shape at age 14 and 18 between individuals born preterm (cases) with those born full-term, stratified by sex. Linear regression coefficients from all HSMs were simultaneously entered into Shape software, to model overall differences in hip shape.

Supplementary Figure 2. Composite hip shape figures representing differences in proximal femur shape at age 14 and 18 between individuals presenting as breech (cases) vs. non-breech, stratified by sex. Linear regression coefficients from all HSMs were simultaneously entered into Shape software, to model overall differences in hip shape.